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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MCGARRY, SEAN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 03/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/808,743	PEDERSEN ET AL.	
	Examiner	Art Unit	
	Sean R McGarry	1635	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-18 and 27-33* is/are pending in the application.

4a) Of the above claim(s) *4,5,17,18 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 6-16, 27, 28, , and 30-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant has added new claims 27-33 in the response filed 10/20/03. Claim 29 is directed to a non-elected invention and has been withdrawn from consideration. Claim 27 recites subject matter from both Groups I and II with claims 28 and 30-33 being generic to both inventions. Claims 27, 28 and 30-33 are examined only so far as they read on the elected subject matter.

Claims 1-3, 6-16, 27, 28, and 30-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Both claims 1 and 27 recite the following ". . .contacting the cells with a proliferation inhibitory effective amount of an antisense polynucleotides or oligonucleotide that hybridizes with a mRNA encoding the Type . . . under conditions that allow hybridization of the antisense polynucleotides with the mRNA. . ." The language is not clear and renders the claims vague and indefinite. It is not clear, for example, how one would determine the conditions of administering the oligonucleotide when its conditions would be dependent on the condition required for hybridization of the polynucleotide which, in the context of the claim, polynucleotide is not used when the alternative oligonucleotide is used in the method, for example. The remainder of the claims are rejected as they depend from claims 1 and 27.

Claims 1-3, 6-16 remain rejected and new claims 27, 28, and 30-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the inhibition of growth of AS-30D hepatoma cell line in culture via the expression of SEQ ID 1 in antisense orientation, does not reasonably provide enablement for the full scope instantly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. This rejection is maintained for the same reasons of record set forth in the Official Action mailed 7/25/03.

The instantly claimed invention is drawn to the inhibition of tumor cell in culture or in a whole animal via the inhibition of a hexokinase a targeted antisense transcript or oligonucleotide (claims 1 and 6-16). The elected invention is drawn to inhibition via antisense targeted to a type II hexokinase including SEQ ID NO: 1. The instant invention reads on antisense-based therapy of cancer. These cancers include tumors in tissues of brain, colon, urogenital, lung, renal, prostate, pancreas, liver, esophagus, stomach, hemotopoietic, breast, thymus, testis, ovary, and uterus. The invention also includes the treatment of cancers such as low grade astrocytoma, anaplastic astrocytoma, glioblastoma, medulloblastoma, gastric cancer, hepatoma, colorectal cancer, colorectal adenoma, acute myelogenous leukemia, lung cancer, renal cancer, leukemia, breast cancer, endometrial cancer, bone cancer, squamous cell cancer and neuroblastoma. The breadth of cancers contemplated for treatment is indeed vast.

The instant specification shows the inhibition of AS-30D hepatoma cells in culture upon their transfection with an antisense Type II hexokinase (SEQ ID NO:1) expression

vector. It has been shown that expression of SEQ ID NO: 1 in antisense orientation can inhibit AS-30D cell growth. The specification fails to show how the inhibition of a Type II hexokinase that may also inhibit both a Type I and Type II hexokinase in one cell line correlates to the inhibition of tumor cell growth via the inhibition of any one particular hexokinase in other cells and further in cell of a whole animal. The instant specification indicates that it is "highly likely" that both a Type I and a Type II hexokinase are inhibited by an antisense transcript of SEQ ID NO: 1 (see page 40). The specification therefore fails to demonstrate the inhibition of cell grow is due to the inhibition of either a Type I or Type II hexokinase alone.

Applicants priority document indicates that it is only Type II and to a lesser extent Type I that are over expressed in highly glycolytic tumors. It is further indicated that the experiments, which parallel those of the instant specification were designed to inhibit both Type I and Type II hexokinase (see page 3 of the priority document, for example). The instant specification has failed to show a correlation that hexokinase overexpression, for example, is causative of the broad range of cancers instantly considered for treatment.

Newgard et al (US 5,891,717) states at column 17 "[h]owever, the correlation [increases in low Km hexokinase activity correlation with cell transformation] has not been proven to exist as a cause and effect relationship." This would indicate that one in the art would be required to determine the relationship of any particular hexokinase with any particular cancer to determine its suitability as a target for the treatment of a vast array of cancers, for example.

Furthermore the art of antisense-based therapy is in general an unpredictable art where the instant specification provides no specific guidance for the treatment of any specific cancer by targeting any particular hexokinase, for example. Branch [TIBS Vol. 23, February 1998] addresses the unpredictability and the problems faced in the antisense art with the following statements: "[a]ntisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. [h]owever, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "[t]o minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. [t]his is a challenging quest."; "[h]owever, their unpredictability confounds research applications of nucleic acid reagents."; "[n]on-antisense effects are not the only impediments to rational antisense drug design. [t]he internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,. . ."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. [a]ntisense compounds are no exception. [a]s is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response

curve and therapeutic index is known."; [c]ompared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "[b]inding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. [s]ince accessibility cannot be predicted, rational design of antisense molecules is not possible."; and, "[t]he relationship between accessibility to ODN binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored. . . [i]t is not yet clear whether *in vitro* screening techniques. . . will identify ODNs that are effective *in vivo*."

Jen et al [STEM CELLS Vol. 18:307-319, 2000] discuss antisense-based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al discuss the advances made in the art but also indicate that progress needs to be made in the art. In the conclusion of their review Jen et al assert "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated "[t]he key challenges to this field have been outlined above. [I]t is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. [a] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising

form of therapy." It is clear from Jen et al that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

Agrawal [TIBTECH, Vol. 14:376-387, October 1996] states the following: " [t]here are two crucial parameters in drug design: the first is the identification of an appropriate target in the disease process, and the second is finding an appropriate molecule that has specific recognition and affinity for the target, thereby interfering in the disease process" (page376); "[o]ligonucleotide must be taken up by cells in order to be effective. [s]everal reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is a complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum . . .[i]t is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency." (Page 378); "[m]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page379); "[a]ny antisense activity observed in such artificial systems [cell culture] should be scrutinized carefully with respect to the disease process and its applicability to *in vivo* situations." (Page 379).

The instant specification fails to provide any particular target for any particular disease and further has not provided any specific guidance on how to make an antisense that would be predictably effective for treating any of the vast array of

diseases instantly contemplated. One in the art would be left to determine all of these determinations by engaging in undue trial and error experimentation, for example.

Applicant's arguments filed 10/20/03 have been fully considered but they are not persuasive.

Applicant argues that the vast range of cancers contemplated in the claimed invention all share the common characteristic of having a "highy glycolytic" phenotype due to hexokinase activity. Applicant also argues that the reliance on Newgard in the Action appears to aknowledge a correlation between hexokinase and cell proliferation. It is noted that the assertion of Newgard is that any cell might be inhibited by the inhibition of a hexokinase. In the context of a cancer treatment, this assertion could be problematic when taken in context of the sate of the art of antisense therapies. For example, how would one inhibit only tumor cells and not all cells when considering applicants reliance on Newgard?

Applicant argues that there is no basis for the Actions assert that a correlation has not been established for the inhibition of Type 1 and Type II hexokinase vs. inhibition of Type I or Type II. Applicant is again directed to their priority document that clearly indicates that the methods used in the instnt specification were specifically designed to inhibit both Type I and Type II hexokinase. There has been no showing of the inhibition of only Type I or Type II in the instant specification and the Exhibits provided by applicant do not show the correlation either. There is no indication in the Exhibits what Type or Types of Hexokinase are inhibited, for example. The evidence

that applicant relies on from the specification and from the Exhibits does not show the inhibition of only a Type II hexokinase where there has been a correlation shown for inhibition of tumor cell growth. Applicant argues that this line of argument appears to be based on a requirement for knowledge of mechanism. This, however, is not the case since such inhibition of only Type II has simply not been demonstrated. Applicant argues that one in the art would know based on the homology of Type I and Type II hexokinases that an antisense molecule based on either hexokinase [Type I or Type II] likely would inhibit the activity of both. It is noted that this cross inhibition is not necessarily true for all antisense and further is not required by the claims.

Claims 1-3, 6-16, 27, 28, and 30-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification discloses SEQ ID NO: 1, which corresponds to the cDNA of the human species of Type II hexokinase. The claimed invention is drawn to the inhibition of a Type II hexokinase via antisense in a method of treating a vast range of cancers. The claims are so broad as to embrace encompass the inhibition corresponding sequences from other species, mutated sequences, allelic variants, splice variants, sequences that have a recited degree of identity (similarity, homology), and so forth and the treatment of any cancer that may have a "highly glycolytic phenotype". The methods require the

use of antisense oligonucleotides which structures have not been disclosed. The specification does not disclose the sequence (ie structure) of any other antisense molecule other than the full expressed SEQ ID NO: 1 in antisense orientation. The specification fails to first describe the structure of the vast range of possible targets and second fails to provide the structure of antisense molecules that have a structure that has been shown by the specification of the art to correlate with the function of inhibiting tumor cell growth. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Although the specification may provide a method to find potential antisense inhibitors, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that

it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

The species specifically disclosed are not representative of the genus because the genus is highly variant where, for example there has been no establishment of a structure known in the art or shown by the specification to correlate with the specific function of inhibiting a hexokinase such that a tumor cell is inhibited, especially in the context of treating a disease. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

The species exemplified in the application, for example, inhibits both Type I and Type II hexokinase, while the scope of the instant invention embraces the inhibition of only a Type II hexokinase. There have been no such species described in the instant application.

It is noted that in making the above rejections claims 2 and 28 have been interpreted to not be limited to antisense that are fully complementary to region SEQ ID NO: 1. The claims require only that the antisense be complementary to a sequence set forth in SEQ ID NO: 1. The antisense therefore could be complementary to two nucleotides of SEQ ID NO: 1 but further complementary to some other hexokinase, for example.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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